Topic 19 – Electrophysiology, rythmology and pacing – D

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0298

Action potential shortening in the pig right ventricular outflow tract epicardium

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The right ventricular outflow tract (RVOT) has a distinct embryological origin from the rest of the right ventricle (RV) and is a frequent origin for idiopathic and disease-related arrhythmias. We hypothesised that heterogeneous action potential duration (APD) across the right ventricle (RV) may contribute to RVOT arrhythmia generation. Pigs were anesthetized and monophasic action potentials (MAPs) recorded in sinus rhythm from the epicardium of the RV free wall and RVOT. The RV was isolated and perfused via both right and left anterior coronary arteries. The preparation was paced (1-5Hz) and the electrical activity optically mapped (di-4-ANEPPS, 10μM) on both epicardial (EPI) and endocardial (ENDO) surfaces. The expression of potassium channels was assessed by RT-PCR. In vivo, MAP durations measured at 20% and 80% repolarization were both significantly shorter in the RVOT than in the RV free wall EPI (P<0.05). Similar APD variations were observed ex vivo as RVOT APD20 and APD80 were decreased by 29% and 15% respectively compared to free wall (P<0.01). Interestingly, no APD difference was observed on the ENDO resulting in a larger transmural APD difference in the RVOT than in the RV free wall. The RVOT EPI APD80 shortening was preserved over a range of stimulation frequencies leading to a downward shift of the restitution curve and a significant decrease of its slope (P<0.05).In accordance with these results, expression level of mRNA coding for Kv4.3 (Ito) and Kv11.1 (IKr) were upregulated in the RVOT compared to the RV free wall epicardium (P<0.01) while no difference was found for Kv7.1 (IKs) or Kv4.2 (Ito). Moreover, no variation in K+ channel expression was observed across the RV endocardium. Action potentials are shorter in the RVOT than elsewhere in the RV EPI. This electrophysiological signature was mirrored by regional variations in specific K+ channels. The resulting APD dispersion may facilitate RV re-entrant arrhythmias in the context of a RVOT ectopy.

0196

Cholinergic and adrenergic stimulation in sheep left atria: modulation of action potential duration heterogeneity

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Introduction: Electrophysiological heterogeneity is well known to play a role in arrhythmogenesis and the maintenance of atrial fibrillation. However, the impact of cholinergic and adrenergic stimulation on action potential duration (APD) heterogeneity has not yet been characterized in detail. The goal of this study was therefore to investigate APD heterogeneity in sheep left atria (LA) upon cholinergic and adrenergic stimulation and the role of electrophysiological and structural heterogeneity which are evocated in the genesis and maintenance of atrial fibrillation

Methods: Combined optical mapping and microelectrode experiments were performed in circumflex artery-perfused LA preparations from sheep. The atria were paced on the endocardial surface from 0.5 to 6Hz from the LA appendage (LAAEN), pulmonary vein ostia (PVEN) or LA roof (LAREN). Following control recordings (CON), the left atria were perfused with acetylcholine (Ach, 5 μM) and/or isoprenaline (Iso, 5 μM). APD80 was measured from LAAEN, PVEN and LAREN endocardium in each condition.

Results: In CON, when pacing LAAEN at 1Hz, we found the longest APD80 in PVEN (227±9ms, P<0.05, N=28) compared to LAAEN (199±9ms, N=23) and LAREN (218±14ms, ns, N=19). Upon addition of Ach, APD80 was reduced overall by 33% when addition of Iso reduced APD80 by 47%. The effect of Ach was the strongest in LAAEN (37 % reduction) compared to the other two regions (30% and 33%, P<0.05). Combination of Ach and ISO reduced overall APD80 by 10% compared to Ach alone. In all case, Iso resulted in loss of APD heterogeneity across the different regions.

Conclusion: Our results indicate that electrophysiological heterogeneity in the intact sheep left atrium may contribute to the mechanisms underlying the genesis and maintenance of AF.

0456

Comparison of spontaneous calcium release events in pulmonary vein and left atria cardiomyocytes

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Pulmonary veins (PV) have been involved in the onset of atrial fibrillation in humans. In rat, we reported a catecholaminergic automatic activity in PV cardiomyocytes (CM) and not in the left atria (LA). Our objective was to identify differences in calcium cycle between PV and LA CM which could explain the arrhythmogenic potential of PV since cytoplasmic calcium oscillations precede variations of membrane potential which are involved in arrhythmias.

Confocal fluorescence imaging was performed in rat isolated CM with di-8-ANEPPS to study tranverse tubule organization, with specific antibodies for ryanodine receptors and L-type calcium channels (RyR-Cav1.2) coupling, with fluo-4 for spontaneous calcium events (SCaE) frequency determination and calcium transient amplitude. Calcium current was recorded with a whole-cell patch clamp technique.

Spontaneous calcium events frequency was significantly (p<0.001) higher in PV than in LA CM (15,7 ± 0,7 SCaE/100μm/sec, n= 132 vs 10,9 ± 0,7 SCaE/100μm/sec, n= 120). This can be associated with 1) a higher percentage of cells showing a transverse tubule organization in PV than in LA CM (61,6 %,n=86 vs 21,2 %, n=85; P<0.001) and among these cells, 2) a better tranverse tubule organization in PV than LA CM (power = 47,6 ± 0,7, n= 86 vs 43,2 ± 0,9, n= 26; P<0.01) and 3) a better RyR-Cav1.2 coupling in PV compared to LA. Moreover, in patch-clamp experiments, we showed a significantly (p<0.001) higher density of calcium current in PV than in LA CM (4.81 ± 0,29pA/pF, n=30 vs 3.00 ± 0,28pA/pF, n=20). A 63 % increase of the calcium transient amplitude was observed in PV compared to LA CM and this was associated with a more important sarcomere shortening (x 4.8, n=7 for LA and 31 for PV).

In conclusion, the tranverse tubule organization associated with more important calcium exchanges support the higher spontaneous calcium events frequency observed in PV CM. This could be related to the arrhythmogenic potential of PV CM.

0151

Role a calcium/calmodulin-dependent serine protein kinase on Cav1.2 channel regulation

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Background: Voltage-dependent calcium channels (Cav) constitute a major pathway for the entry of calcium into excitable cells. The long list of cardiac pathologies highlights the key role played by Cav1.2 channels in cardiac physiology. A calcium/calmodulin-dependent serine protein